Extraskeletal Myxoid Chondrosarcoma

"An indolent, but resilient and capricious tumor"

Saleh G, Evans HL, Ro JY, Ayala, Cancer 1992

Roberta Maestro, CRO Aviano National Cancer Institute

Nothing to disclose

Roberta Maestro, CRO Aviano National Cancer Institute

Extraskeletal myxoid chondrosarcoma

First described by Stout and Verner[1953] as “chondrosarcoma of the extraskeletal soft tissues”

Named “extraskeletal myxoid chondrosarcoma” by Enzinger and Shiraki[1972]

aka “chordoid sarcoma” or member of the “tenosynovial sarcoma family”, together with synovial sarcoma, epitheliod sarcoma, clear cell sarcoma)

Epidemiology

Rare tumor (<3% of soft tissue sarcomas).

Middle aged/older adults (median age 57y), rare in children and adolescents.

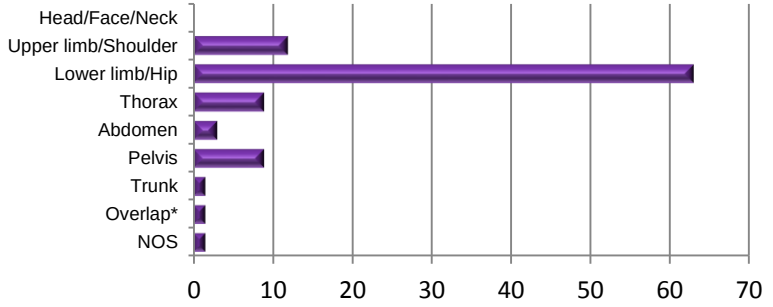
Predilection for male patients (male-to-female ratio 2:1).

Clinical features

Limb and limb girdles

Usually painless

About 13% of pts present with metastases



Pathologic features

-well circumscribed mass with thin pseudocapsule

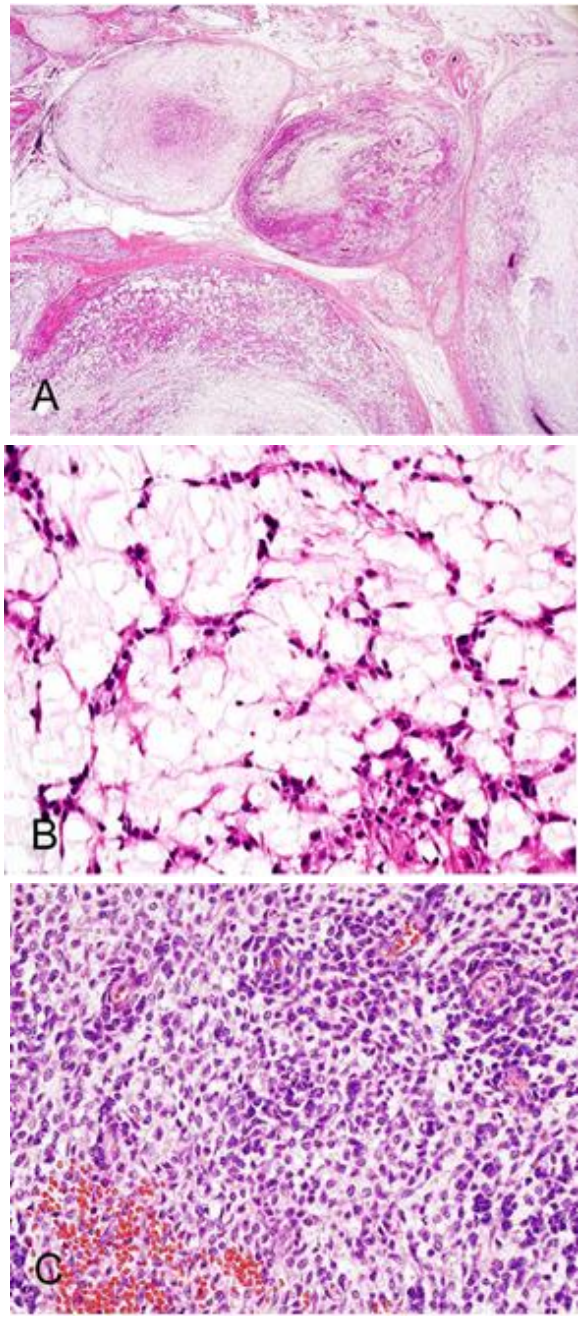
-spindled to epitheliod cells arranged in cords, strands or clusters

-moltilobular architecture (Fig A)

-abundant myxoid matrix (Fig B)

- infrequent mitosis, but in high-grade hypercellular forms (Fig C)

-intratumor haemorragic areas and cystic cavities, sometime necrotic



EMCS's features:
A Multinodular growth;
B Hypocellular nodules formed by hypovascular myxoid matrix
C Hypercellular, high-grade EMCS;

From Romeo and Dei Tos, Virchows Arch. 2010

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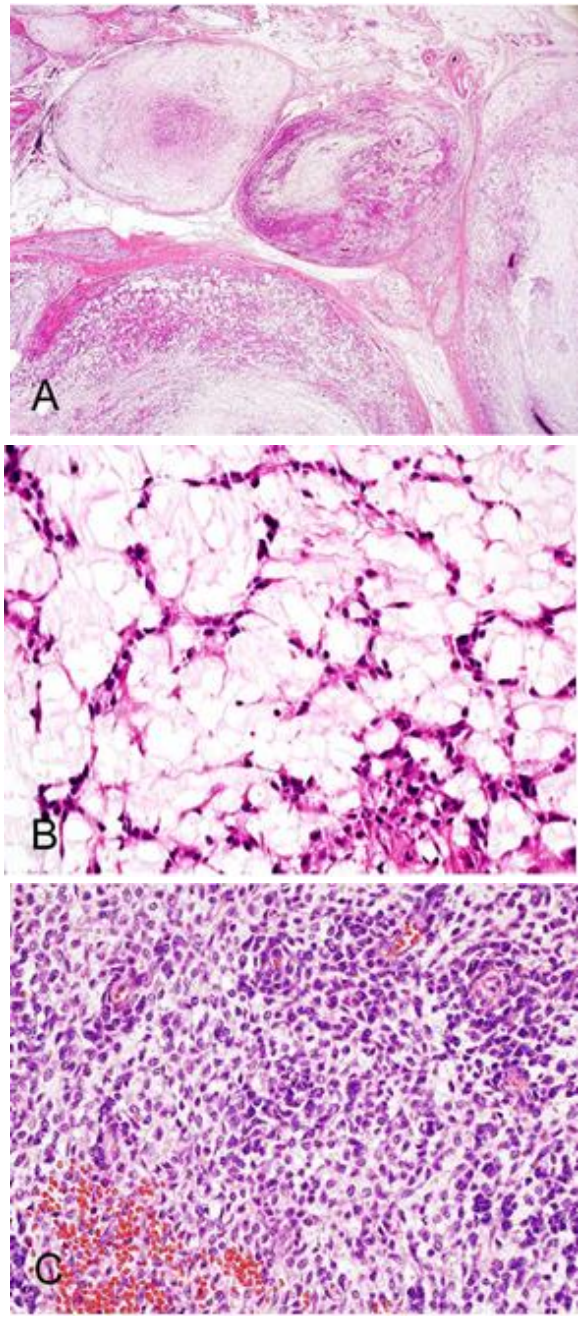
-intratumor haemorragic areas and cystic cavities, sometime necrotic

-**NO CLEAR EVIDENCE OF CARTILAGINEOUS DIFFERENTIATION**



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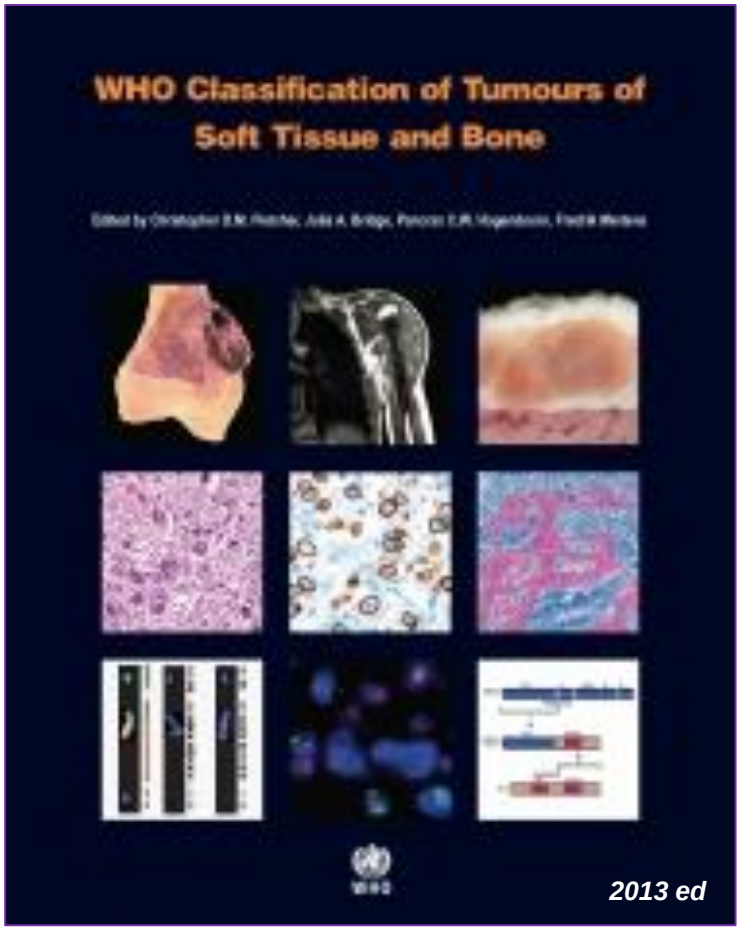

Chapter 12

Tumours of uncertain differentiation

Acral fibromyxoma
Intramuscular myxoma
Juxta-articular myxoma
Deep ("aggressive") angiomyxoma
Pleomorphic hyalinizing angiectatic tumour of soft parts
Ectopic hamartomatous thymoma
Atypical fibroxanthoma
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumour
Myoepithelioma/myoepithelial carcinoma/mixed tumour
Haemosiderotic fibrolipomatous tumour
Phosphaturic mesenchymal tumour
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
➡ **Extraskeletal myxoid chondrosarcoma**
Malignant mesenchymoma
Desmoplastic small round cell tumour
Extrarenal rhabdoid tumour
PEComa
Intimal sarcoma

Chapter 15

Chondrogenic tumours

Osteochondroma
Chondromas: enchondroma, periosteal chondroma
Chondromyxoid fibroma
Osteochondromyxoma
Subungual exostosis and bizarre parosteal osteochondromatous proliferation
Synovial chondromatosis
Chondroblastoma
Chondrosarcoma (grades I–III) *[including primary and secondary variants and periosteal chondrosarcoma]*
Dedifferentiated chondrosarcoma
Mesenchymal chondrosarcoma
Clear cell chondrosarcoma

Extraskeletal myxoid chondrosarcoma

Genetics

Simple karyotype sarcoma characterized by a balanced chromsomal translocation

2/3 of the cases	t(9;22)(q22;q12)	**EWSR1-NR4A3**
1/3 of the cases	t(9;17)(q22;q11)	**TAF15-NR4A3**
rarer	t(9;15)(q22;q21)	**TCF12-NR4A3** *(TCF12, bHLH TF)*
	t(3;9) (q12;q31)	**TFG-NR4A3** *(TFG, TRK-Fused Gene)*

Extraskeletal myxoid chondrosarcoma

Genetics

Simple karyotype sarcoma characterized by a balanced chromsomal translocation

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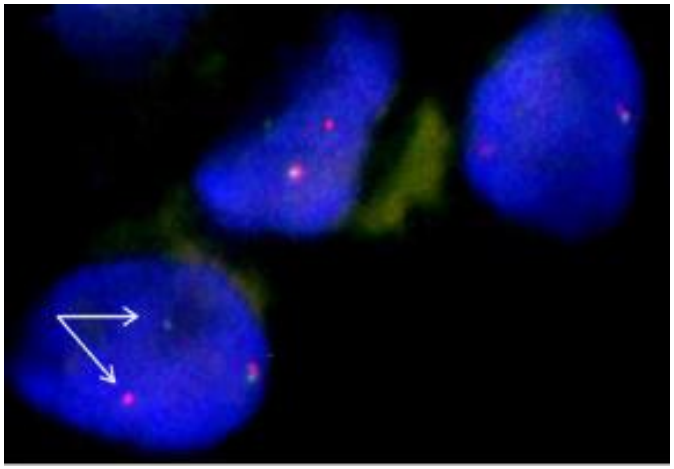
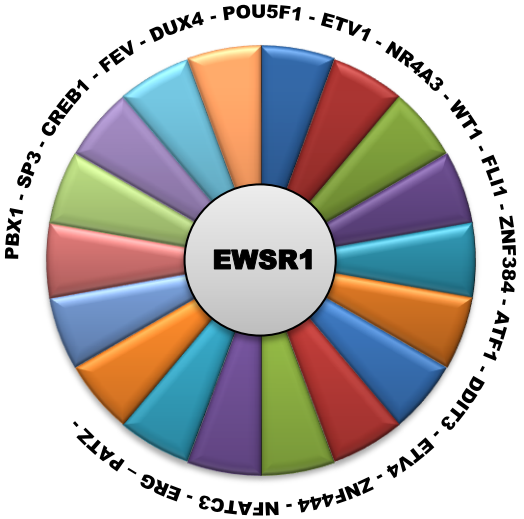
	t(3;9) (q12;q31)	**TFG-NR4A3**



NR4A3 break apart



Extraskeletal myxoid chondrosarcoma

Differential diagnosis

Myoepithelial neoplasms

Myxoid liposarcoma

Low-grade myxofibroma

Ossifying fibromyxoid tumor (OFMT)

High-grade (hypercellular) EMCS

Myoepithelial carcinoma

Malignant melanoma

Metastatic carcinoma

Proximal-type epitheliod sarcoma

Hornick JL Practical Soft Tissue Pathology, 2013 Elsevier

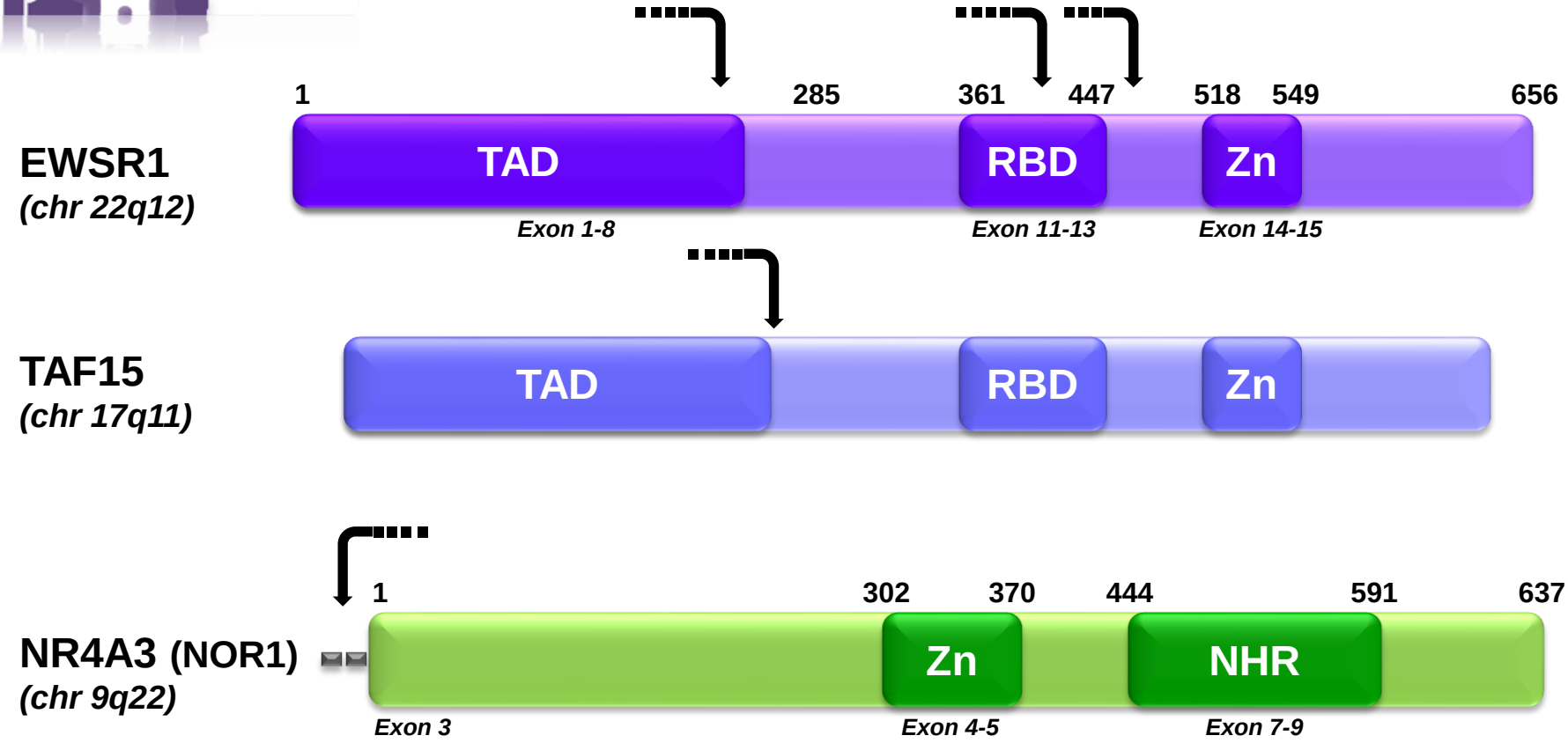
Extraskeletal myxoid chondrosarcoma

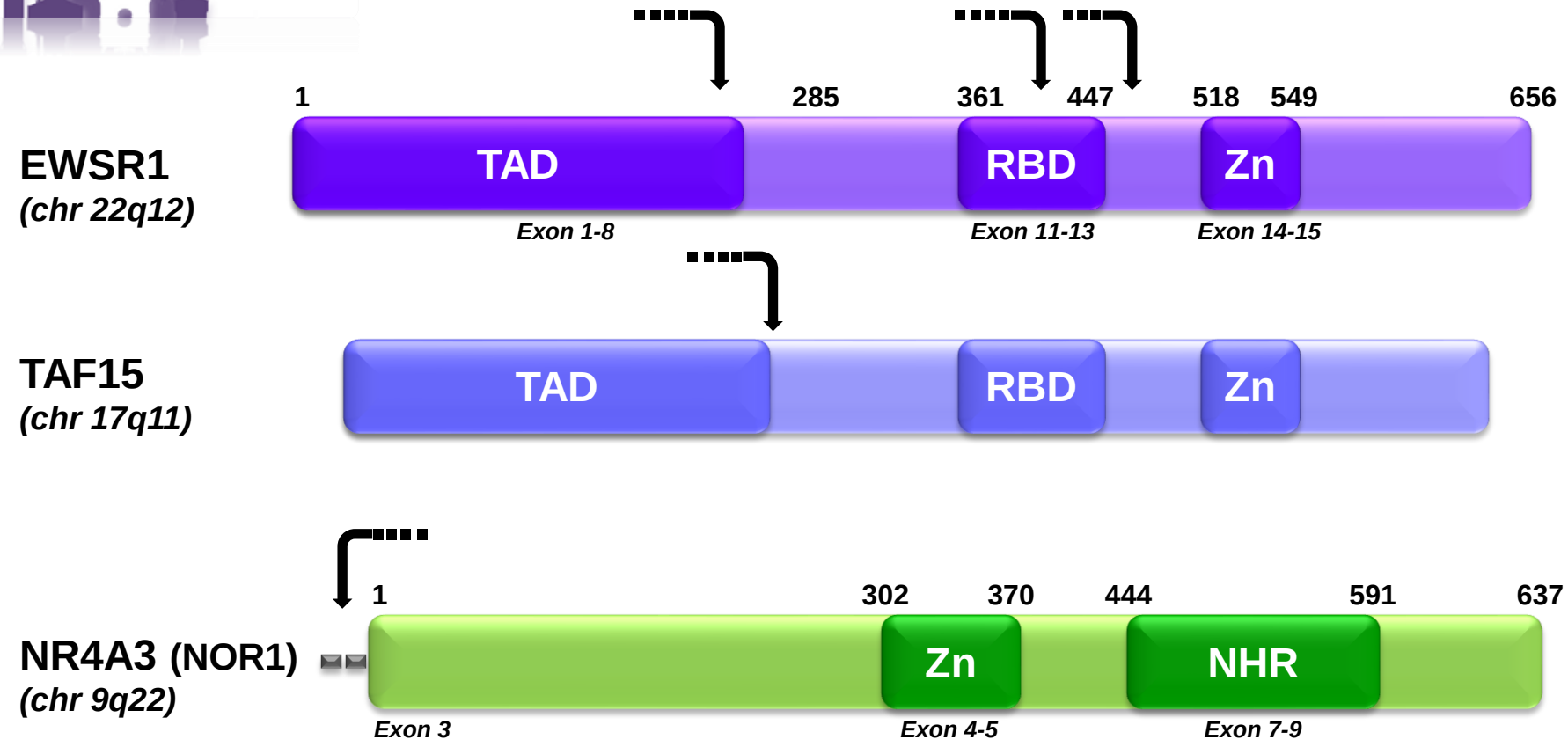
NR4A3/NOR1/CHN

Transcription factor of the orphan nuclear hormone receptor family (steroid steroid-thyroid hormone-retinoid receptor superfamily).

EWSR1 and TAF15

RNA binding proteins involved in RNA processing, gene expression, cell signaling, alternative splicing, DNA damage response.


EWSR1
(chr 22q12)
1
285
361
447
518
549
656
TAD
RBD
Zn
Exon 1-8
Exon 11-13
Exon 14-15
TAF15
(chr 17q11)
TAD
RBD
Zn
NR4A3 (NOR1)
(chr 9q22)
1
302
370
444
591
637
Zn
NHR
Exon 3
Exon 4-5
Exon 7-9



EMCS chimera

Extraskeletal myxoid chondrosarcoma

Treatment

Standard treatment: radical local excision (negative margins) ± RT

High incidence of local recurrences (35-50%) and
distant metastases (25-50%), even >15y after diagnosis

Overall survival: ~90% @ 5y; ~ 70% @ 10y; ~ 60% @ 15y

"An indolent, but resilient and capricious tumor" *Saleh et al., Cancer 1992*

Extraskeletal myxoid chondrosarcoma

Chemotherapy

Study	Regimen	CR	PR	SD	PD	Disease control rate
Patel et al., 1995	Doxorubicin ± Dacarbazine and Cyclophosphamide			13	9	59% (13/22)
McGrory et al., 2001	Multi-agent	1	1		4	33% (2/6)
Drillon et al., 2008	Different regimens, mostly anthracycine-based			21	11	66% (21/32)
Ogura et al., 2012	Ifosfamide-based			1	3	25% (1/4)
Stacchiotti et al., 2013	Epirubicin ± Ifosfamide		4	3	3	70% (7/10)

Cureus
2015 Dec 24;7(12):e432

Open Access Case Report

DOI: 10.7759/cureus.432

Unresectable Extraskeletal Myxoid Chondrosarcoma of the Neck: Early Tumor Response to Chemoradiotherapy

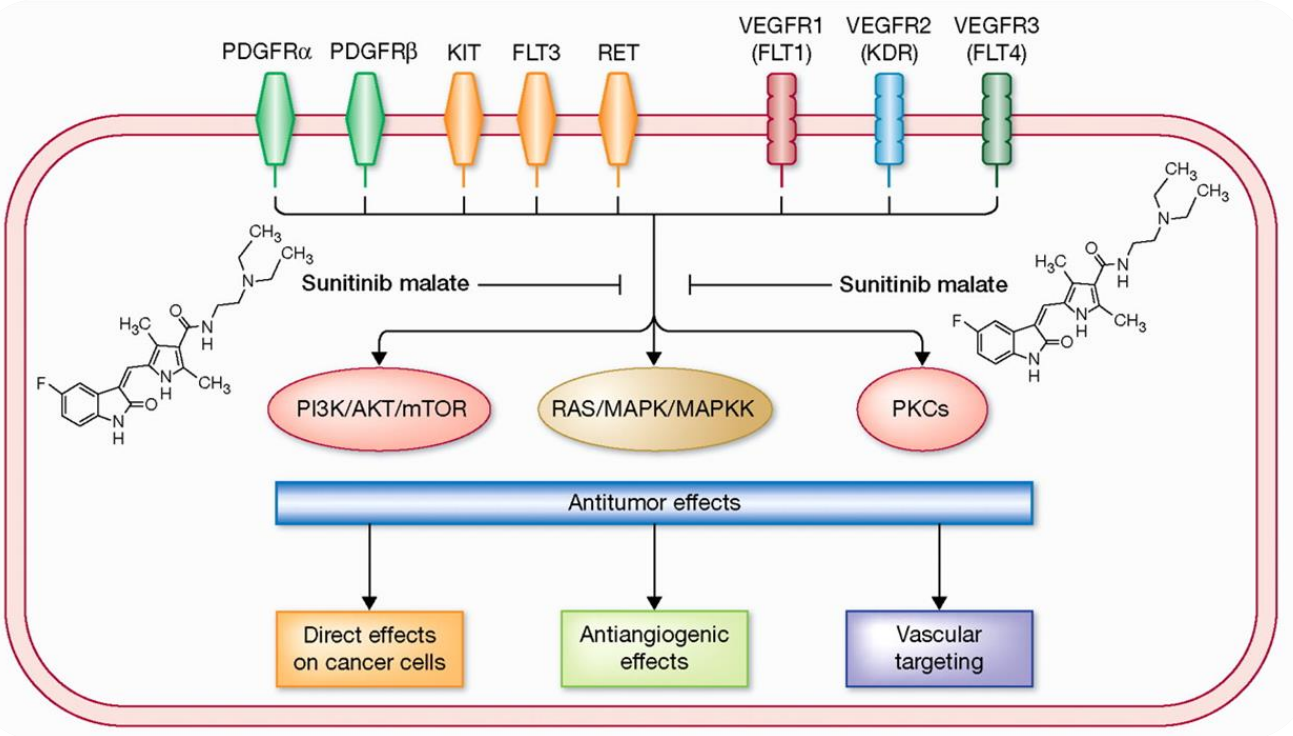
Mark Zaki [1], Pam Laszewski [1], Natasha Robinette [2], Husain Saleh [3], Naweed Raza [4], Ammar Sukari [5], Harold Kim [1]

Abstract

Extraskeletal myxoid chondrosarcoma (EMC) rarely occurs in the head and neck and is generally managed with primary surgery. To our knowledge, no cases of unresectable EMC of the neck have been reported. We present a case of an unresectable EMC treated with chemotherapy and radiation, and highlight the exceptional early response to therapy.

Extraskeletal myxoid chondrosarcoma

Sunitinib



	IC_{50} (nM)	
Target	**Sunitinib**	**Pazopanib**
VEGFR-1	**2**	**10**
VEGFR-2	**10**	30
VEGFR-3	**17**	47
PDGFR-β	**8**	84
EGFR	880	—
c-KIT	**10**	74
FGF-1R	880	**14**
FLT-3	**14**	—
CSF-1R	100	—
Raf-1	—	—

VOLUME 27 · NUMBER 19 · JULY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Phase II Trial of Sunitinib in the Treatment of Nongastrointestinal Stromal Tumor Sarcomas

Suzanne George, Priscilla Merriam, Robert G. Maki, Annick D. Van den Abbeele, Jeffrey T. Yap, Timothy Akhurst, David C. Harmon, Gauri Bhuchar, Margaret M. O'Mara, David R. D'Adamo, Jeffrey Morgan, Gary K. Schwartz, Andrew J. Wagner, James E. Butrynski, George D. Demetri, and Mary L. Keohan

Purpose
To evaluate the potential benefit of continuous daily dosing sunitinib in patients with advanced nongastrointestinal stromal tumor (GIST) sarcomas.

Patients and Methods
A total of 53 patients with advanced non-GIST soft tissue sarcomas received sunitinib 37.5 mg daily. Primary end point was Response Evaluation Criteria in Solid Tumors defined response. Secondary end points were stable disease at 16 and 24 weeks. [^{18}F]-fluorodeoxyglucose positron emission tomography was performed on a subset of 24 patients at baseline and after 10 to 14 days of therapy.

Results
Forty-eight patients were eligible for response. One patient (desmoplastic round cell tumor [DSRCT]) achieved a confirmed partial response (PR) and remained on study for 56 weeks. Ten patients (20%) achieved stable disease for at least 16 weeks. Metabolic PR was seen in 10 (47%) of 21 of patients. Metabolic stable disease was seen in 11 (52%) of 21. There were no unexpected toxicities observed.

Conclusion
Sunitinib demonstrated notable evidence of metabolic response in several patients with non-GIST sarcoma. The relevance of disease control observed in subtypes with an indolent natural history is unknown, however, the durable disease control observed in DSRCT, solitary fibrous tumor, and giant cell tumor of bone suggests that future evaluation of sunitinib in these subtypes may be warranted.

Sunitinib activity in Soft Tissue Sarcomas

Study	Sarcoma subtype	Best response
Stacchiotti et al., 2011	Alveolar soft part sarcoma	5 PR, 3 SD, 1 PD
Stacchiotti et al., 2012	Solitary Fibrous Tumor	2 PR, 16 SD, 13 PD
Levard et al., 2013	Solitary Fibrous Tumor	3 SD, 1 PD with Sunitinib *(2 SD, 4 PD with Pazopanib)*
Italiano et al., 2013	Desmoplastic round cell tumor	2 PR, 3 SD, 3 PD

SARCOMA AND GIST CONFERENCE
Milan Italy
16-17 FEBRUARY 2016

Stacchiotti et al. Clinical Sarcoma Research 2012, 2:22
http://www.clinicalsarcomaresearch.com/content/2/1/22

CLINICAL SARCOMA RESEARCH

CASE REPORT Open Access

Extraskeletal myxoid chondrosarcoma: tumor response to sunitinib

Silvia Stacchiotti[1*], Gian Paolo Dagrada[2], Carlo Morosi[3], Tiziana Negri[2], Antonella Romanini[4], Silvana Pilotti[2], Alessandro Gronchi[5] and Paolo G Casali[1]

Abstract

Background: Extraskeletal myxoid chondrosarcoma (EMCS) is a rare soft tissue sarcoma of uncertain differentiation, characterized in most cases by a translocation that results in the fusion protein *EWSR1-CHN* (the latter even called *NR4A3* or *TEC*). EMCS is marked by >40% incidence of metastases in spite of its indolent behaviour. It is generally resistant to conventional chemotherapy, and, to the best of our knowledge, no data have been reported to date about the activity of tirosin-kinase inhibitor (TKI) in this tumor. We report on two consecutive patients carrying an advanced EMCS treated with sunitinib.

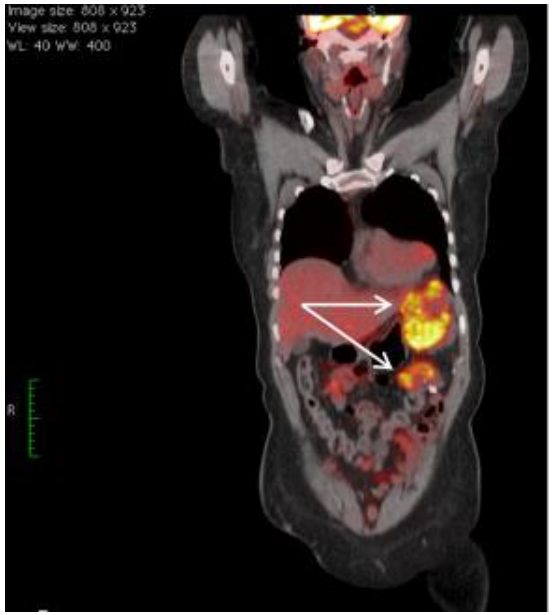
Methods: Since July 2011, 2 patients with progressive pretreated metastatic EMCS (Patient1: woman, 58 years, PS1; Patient2: man, 63 years, PS1) have been treated with continuous SM 37.5 mg/day, on an individual use basis. Both patients are evaluable for response. In both cases diagnosis was confirmed by the presence of the typical *EWSR1-CHN* translocation.

Results: Both patients are still on treatment (11 and 8 months). Patient 1 got a RECIST response after 4 months from starting sunitinib, together with a complete response by PET. An interval progression was observed after stopping sunitinib for toxicity (abscess around previous femoral fixation), but response was restored after restarting sunitinib. Patient 2 had an initial tumor disease stabilization detected by CT scan at 3 months. Sunitinib was increased to 50 mg/day, with evidence of a dimensional response 3 months later.

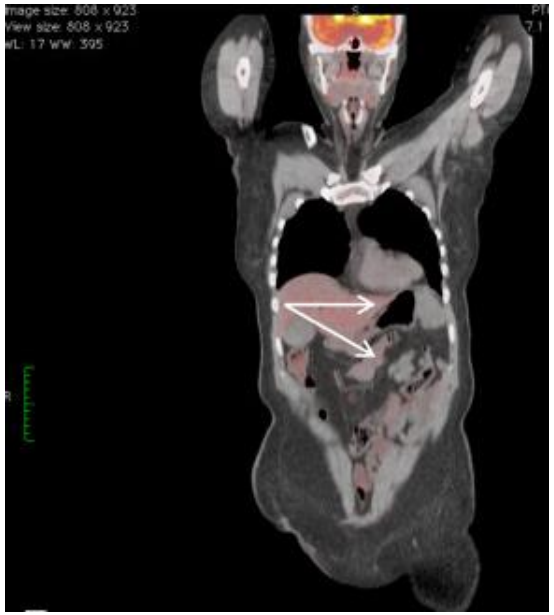
Conclusions: Sunitinib showed antitumor activity in 2 patients with advanced EMCS. Further studies are needed to confirm these preliminary results.

Keywords: Sarcoma, Myxoid extraskeletal chondrosarcoma, Sunitinib malate, Targeted therapy, Chemotherapy

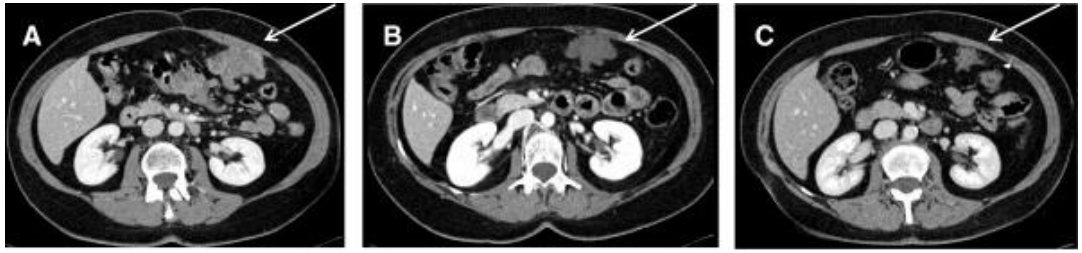
Extraskeletal myxoid chondrosarcoma



Baseline



+ 1 mos



Baseline + 1 mos + 4 mos

Stacchiotti et al., Clin Sarcoma Res, 2012

Extraskeletal myxoid chondrosarcoma

SUNITINIB IN EMCS

Named-use program

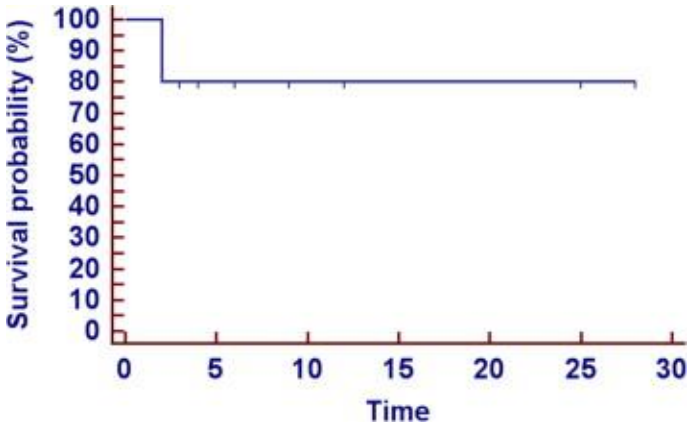
(INT Milano, July 2011-December 2015)

11 pts with progressive advanced EMCS
(37.5 mg/day ; 50 mg/day in the case of primary progression and acceptable toxicity)

Best RECIST reponse:
6 PR, 3 SD, 2 PD

6 pts stopped treatment : 3 toxicity, 3 PD (2 prim., 1 sec.)
5 pts still on therapy (range 1-54+ mos)

Median FU 32 mos: median PFS 34 mos,
median OS not reached



(Update of Stacchiotti et al., 2104)

Trial of Pazopanib in Patients With Solitary Fibrous Tumor and Extraskeletal Myxoid Chondrosarcoma

GEIS (Grupo Espanol de Investigacion en Sarcomas)

ClinicalTrials.gov Identifier: NCT02066285
February 14, 2014

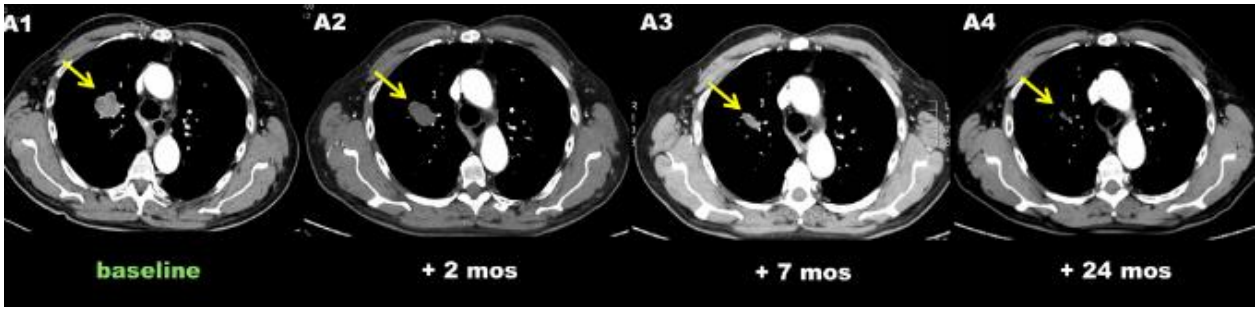
Phase II, open-label, non-randomized, international multicenter clinical trial with two strata (SFT and EMC).

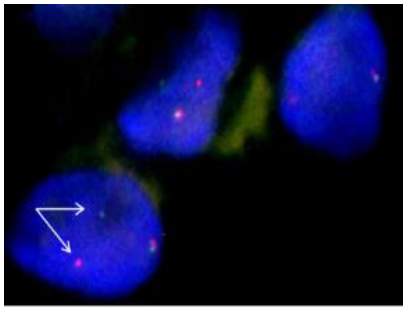
8 sites in Spain, 5 sites in Italy and 5 sites in France.
Patients will receive oral pazopanib at 800 mg once daily continuously. Patients will continue to receive treatment until there is evidence of progressive disease, unacceptable toxicity, non-compliance, withdrawn consent or investigator decision.

The main goal is to determine the objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]) in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma, using Choi and RECIST 1.1 criteria respectively.

Extraskeletal myxoid chondrosarcoma

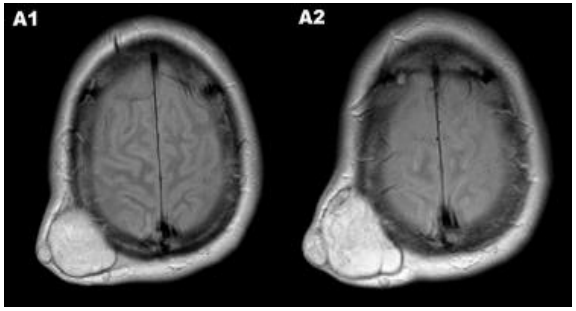
Responders *(8 cases)*

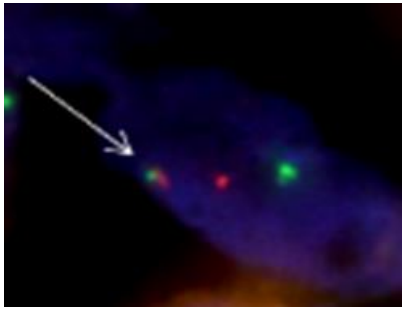




EWS1R-NR4A3

Non responders *(2 cases)*





TAF15-NR4A3

Stacchiotti et al., Eur J Cancer 2014

Extraskeletal myxoid chondrosarcoma

Mechanism of action of sunitinib in EMCS

Does the fusion protein play any role in the response?

Does sunitinib efficacy in EMCS relies
just on an anti-angiogenetic effect
or it targets also EMCS tumor cells?

What are the key mediators of EMCS sensitivity to sunitinib?

EWSR1
(chr 22q12)

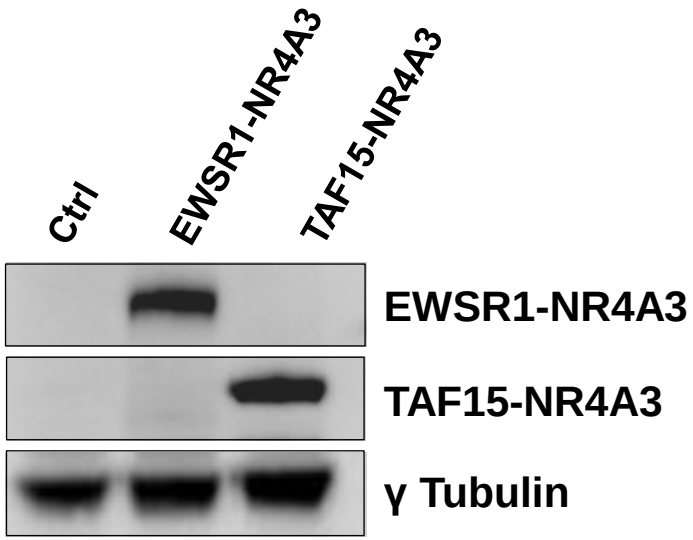
TAF15
(chr 17q11)

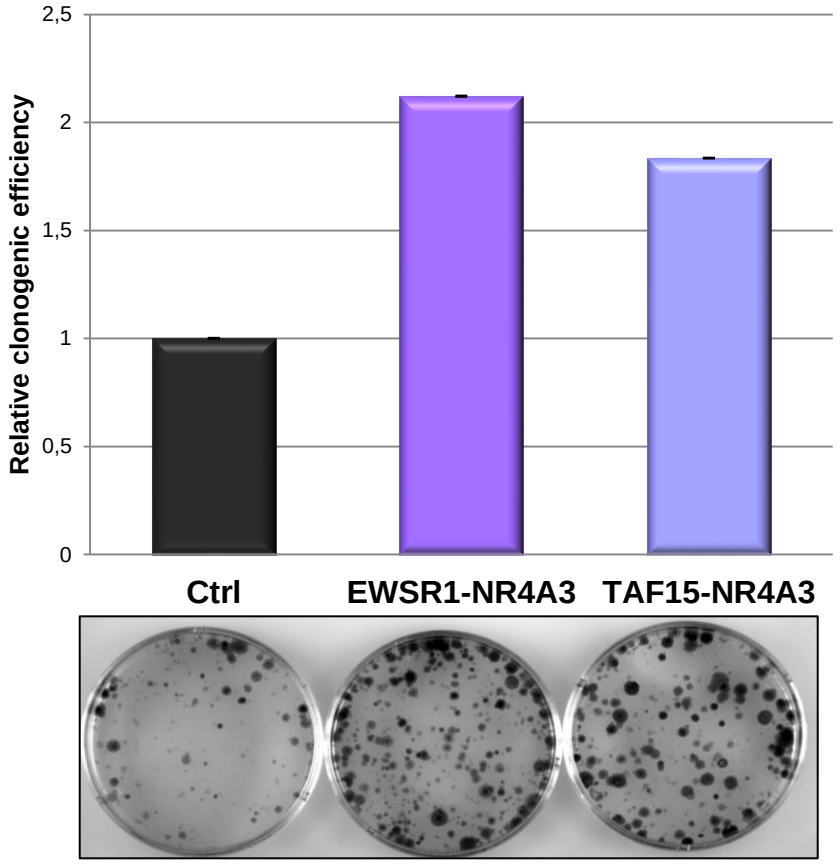
NR4A3 (NOR1)
(chr 9q22)

EMCS chimeras

Cell modeling of EMCS

(EWSR1-NR4A3 and TAF15-NR4A3 engineered cell lines)





Two different cell backgrounds:
HT-1080
BJ E1A/Ras transformed human primary fibroblasts